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13. ABSTRACT (Maximum 200) The work done in this SBIR Phase 1 was to investigate the feasibility of producing a sustain-release injectable gel formulation for Buprenorphine hydrochloride and Buprenorphine free base using Poly-lactide-co-glycolide polymers with various plasticizers and solvents. Our Phase 1 efforts have shown that we can produce gel formulations for both of these molecules that will give prolonged release of the drug from the gel as shown by in-vitro studies. Our studies have demonstrated that these polymers can prolong the release of buprenorphine for over 30 days. However, for acute pain relief, release over a period of 24 - 72 hours would be desirable. Our data has shown that with the initial studies conducted here, we can get release of buprenorphine over 24 - 144 hours in-vitro. In-vivo rates should be faster than these and we plan to carry out animal studies to show this. The initial studies also shows that there are a lot of variables in this system that need to be studied and optimized to get the best release profile with the right therapeutic levels released which can be carried out in Phase 2.				
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FOREWORD

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Ashok Patel
PI - Signature

04/17/97
Date

TABLE OF CONTENTS

COVER	i
REPORT DOCUMENTATION PAGE	ii
FOREWORD	iii
TABLE OF CONTENTS	1
INTRODUCTION	2
MAJOR AIMS	3
MATERIALS	4
METHODS	4
RESULTS	7
CONCLUSION AND DISCUSSION	11
FIGURES AND TABLES	14
PERSONNEL	27

Introduction:

This report pertains to our SBIR Contract # DAMD17-96-C-6040 with the Department of the Army. This work was done between August 1996 to date since we did not receive our DEA license until the end of July and an extension was granted to us by the contracting officer for three months.

The work was carried out in our facility and also some of it was carried out in Dr. Shukla's laboratory at the College of Pharmacy, University of Tennessee, Memphis, TN. Dr. Shukla is the company's consultant in the field of sustain-release drug delivery systems and has worked in this field for the last 10 years. The Principal Investigator is Ashok Patel, Ph.D. of Saimol International Inc.

Major aims:

The major aim of this project was to develop the feasibility of developing an injectable biodegradable gel as a sustain-release drug delivery system for Buprenorphine using biodegradable polymers for the control of acute pain due to traumatic injury. Our initial plan was to characterize the physicochemical property of Buprenorphine hydrochloride and buprenorphine free base in terms of particle size and solubility. We also had to develop analytical methods for measuring Buprenorphine concentrations in various fluids for our tests. We also decided to study the glass transition temperatures of our gels as a method of characterizing our gels since the equipment, a Differential Scanning Calorimeter, required to do this was available in Dr. Shukla's lab.

We had proposed to develop gels using biodegradable polymers such as polylactide-co-glycolide (PLGL) or polylactide polymers. Initial proposal was to study both of these to see which polymer would be better for preparing gels of Buprenorphine. However, studies from Dr. Shukla's lab have shown that PLGL with a 50:50 ratio of lactide to glycolide has worked much better than the polylactide polymers so we decided to use only PLGL for our studies. It is also the most widely used biopolymer in the fabrication of controlled release drug delivery system. Three different molecular weights of 50/50 PLGL which have different intrinsic viscosity's were studied for optimization of release of Buprenorphine hydrochloride. The plasticizer that was used for these studies was Acetyl triethylcitrate (ATEC) as it's a colorless liquid with an aqueous solubility of 55 mg/ml. It has an oral rat LD₅₀ of 1,750 mg/kg and is an FDA approved plasticizer.

Since our first report, Capt. Vaughan had pointed out that it would be advantageous to have release of buprenorphine between 48 - 72 hours and not extended periods such as 30 days that we had been looking for. With this in mind, we had to investigate properties of the polymer and the plasticizers to yield formulations that would release the drug much faster. We therefore decided to investigate using polymers with different inherent intrinsic viscosity (molecular weight) as this affects the release rates of incorporated drugs drastically. We also have investigated using different ratios of the polymer:plasticizer as this also affects the release of the incorporated drug. We also had to investigate using other plasticizers such as TEC and Triacetin which are more water soluble than ATEC.

Materials:

All biodegradable polymers such as 50/50 Poly(DL-lactide-co-glycolide), (PLGL) were obtained from Birmingham Polymers Inc, Birmingham, AL. Acetyl triethylcitrate was obtained from Sigma Chemical CO. ST. Louis, MO. Buprenorphine hydrochloride was obtained from Research Biochemicals Inc, Natick, MA. Triethyl Citrate was obtained from Morflex Inc, Greensboro, NC and the Triacetin was obtained from Aldrich Chemical Company, Milwaukee WI. The polylactide-co-glyclide (PLGL) polymers were obtained from Birmingham Polymers Inc., Birmingham AL.

All other general biochemicals were obtained from Sigma Chemical Co, St. Louis, MO or Aldrich Chemical Co, Milwaukee, WI.

Methods:

UV-Visible studies were carried out on a Beckman DU-50 spectrophotometer. HPLC analysis were carried out on a Waters HPLC unit with a UV-Visible detector. Glass Transition Temperatures were measured with Differential Scanning Calorimeter (Perkin-Elmer DSC 7, Perkin-Elmer Corp., Norwalk, CT) in Dr. Shukla's lab. The temperature that the DSC was run at -180°C to -10°C.

In-vitro release studies were done using a Reciprocating Orbital Shaking Incubator with temperature control chamber.

Special teflon cells:

To study the release of the drug from a given amount of gel formulation, **Special teflon cells** as shown in **figure 1**, were made with a cavity of 0.6 sq.cm. to hold the gel in place in the fluid for the drug to diffuse out from the gel. 24 such teflon cells (cylindrical block 2.54 cm. in diameter and 2.54 cm in height with a cavity of 0.88 cm diameter and 0.4 cm deep on the top) were made -- of the same dimensions by a special machine shop. The cavity has a surface area of 0.6 sq. cm that is exposed to the fluid the cells are placed in and is designed to hold 240 mg of the gel formulation. These teflon cells were designed by Dr. Shukla or all his previous studies and we obtained his design for our cells and had ours made to same dimensions as his. This took 3 weeks to do.

Conversion of Buprenorphine HCl to Buprenorphine base:

Our attempt to obtain Buprenorphine free base from Reckitt and Coleman in England were not successful and Captain Vaughan had suggested 2 other companies that he thought would be able to supply some to us. However, both of these companies, namely Diosynth in Chicago and Interchem in NJ, have not been able to do so. The sales manager of Diosynth, Gery Roman even tried to obtain some free base from their manufacturing facility in Europe since we had explained that this was a collaborative project with the DoD. Unfortunately, even that was not possible as their European manufacturing plants only had the hydrochloride salt available. They were not in a position to special order any at the time either. This meant that we had to convert the hydrochloride to the free base ourselves.

Buprenorphine free base was produced by dissolving 2 g. of the buprenorphine hydrochloride in 5 ml of ice-cold 10 mM Phosphate buffer, pH 7.0 and adding 2.5 ml of 0.25 M NaOH dropwise to this while mixing on ice. The buprenorphine hydrochloride reacts with the NaOH and is converted to the free base which precipitates out of the solution.

The precipitate was filtered and washed with 25 ml of ice-cold phosphate buffer to remove any of the unreacted NaOH. This was done by measuring the pH of the wash solution throughout the process and washing with enough excess water even after the pH of the wash solution indicated no more NaOH present in the wash solution. The buprenorphine free base was then air-dried, ground to a fine powder using a cold mortar and pestle and weighed. This yielded 1.45 g of buprenorphine free base which was used for our studies without further characterization.

Preparation of gel formulations:

Gels from the biodegradable polymer PLGL of varying molecular weights was prepared as follows. 2 g of the polymer was dissolved in 2 ml of acetone in a glass beaker using a magnetic stirrer. Then 4 g of ATEC was added to this mixture and stirred for a further 10 min to ensure uniform mixing. This gave a polymer to plasticizer ratio of 33:67 which has been determined to be optimal by Dr. Shukla's studies. The gel was then slowly heated to 65 to 80°C in an oil bath to evaporate the acetone. The formulation was then allowed to cool to RT and weighed. In case of any weight loss, an equivalent amount of plasticizer was added to compensate for any loss of plasticizer in the process. The complete removal of acetone is achieved by this method and was confirmed by thermal analysis in Dr. Shukla's lab. This process normally required between 2.5 to 3 hours to complete. A known quantity of the drug was then added to the gel and mixed thoroughly to yield the drug-loaded gel.

In-vitro release studies:

In-vitro drug release studies were carried for each drug-loaded gel formulation in **triplicate** at 37°C. These were carried out as follows. 240 mg of each drug-loaded gel formulation was accurately weighed and transferred into the cavity of the Teflon cell. The Teflon cells were then carefully placed in 60 ml glass bottles (Qorpak bottle, Baxter Scientific Products, McGraw Park, IL). Into this was added 40 ml of preheated dissolution medium at 37°C. The bottles were then rotated at 125 rpm at 37°C and at periodic time intervals, samples of the dissolution medium were removed using 60 ml disposable plastic syringes. These were filtered when necessary and the absorbance measured at 286 nm to determine the amount of drug released into the medium. The medium was then replaced in the bottle with fresh preheated medium.

RESULTS:

1. UV-Visible Standard Curve:

Using a Beckman DU-50 scanning spectrophotometer, the maximum absorbance wavelength, λ_{max} , was determined to be 286 nm and a standard curve of Buprenorphine hydrochloride concentration versus absorbance was plotted. All studies were carried out by dissolving Buprenorphine hydrochloride in 50 mM Phosphate buffer, pH 7.4 containing 0.9M NaCl and 0.05% thimerosal. The standard curve was carried out at least 4 times to show reproducibility.

2. HPLC Method:

An HPLC method was also tested for measuring Buprenorphine hydrochloride for analysis of drug release studies from in vivo samples. After studying the solubility of Buprenorphine hydrochloride in aqueous buffers to be about 20 mg /ml, we decided to choose a reverse phase C-18 column for setting up an HPLC system for Buprenorphine. Previous publications from various research groups had also shown that this would be a good solid phase and the mobile phase of 50% KH_2PO_4 50 mM and 50% Acetonitrile would give a fairly good chromatographic system. The column we chose was a μ -Bondapak C-18 column of 3.9 mm internal diameter and 30 cm in length and was obtained from Waters Chromatography, Boston MA. The UV detector was set at 254 nm and the flow rate at 0.8 ml/min. The system also consisted of a Water's 510 pump and a model 486 automated injector (712 Waters Intelligent Sample Processor). The resulting chromatogram is shown in **figure 2**.

Buprenorphine hydrochloride has a retention time of 5.8 min and using this system a standard curve for it was set up as shown in **figure 3**.

3. Solubility Studies:

The solubility of Buprenorphine Hydrochloride and free base in the dissolution medium, namely, 80% 50 mM Phosphate buffer, pH 7.4 containing 0.9% NaCl and 0.05% thimerosal and 20% propylene glycol was studied by adding preweighed quantities of the drug in screw-top polyethylene tubes with a known amount of dissolution medium or the plasticizer ATEC. The tubes were capped and placed in a shaking incubator at 25°C and 37°C for 48 hours each. The tubes were centrifuges after the incubation period and the solution analyzed for drug content using the standard curve of absorbance at 286 nm versus concentration.

The buprenorphine hydrochloride was found to have up to 20 mg/ml solubility in the dissolution medium and about 3.5 mg/ml solubility in ATEC, about 4.0 mg/ml solubility in TEC and about 6.0 mg/ml solubility in Triacetin. The solubility of TEC in water is 5.5 g/100ml and that of Triacetin is 8.0 g/100 ml.

The buprenorphine free base was found to have a very low level of solubility in the dissolution medium (less than 1 mg/ml) and was fairly soluble in both ATEC and TEC (up to 50 mg/ml level).

4. Particle Size Analysis:

Particle size analysis of buprenorphine hydrochloride was carried out by suspending the crystals or particles of the drug in mineral oil and studying the suspension under a light microscope (Nikon Microphot FX) at 100-fold and 450-fold magnification and the average particle size measured for at least 200 particle in an average field and the size calculated by a computer (E-machines). This resulted in average particle size of our buprenorphine hydrochloride sample to be 7 microns. There were less than 5% particle over 15 microns in diameter.

5. Preparation of gel formulations:

The gel formulations were prepared as described in the methods section. The different molecular weight PLGL that were used were:

<u>Average mol. wt.</u>	<u>Intrinsic viscosity</u>	<u>Phys. property of gel</u>
1. 12,400	0.20 dL/g	Very flowable liquid
2. 44,000	0.59	Viscous liquid
3. 116,000	1.15	Viscous gel

The drug levels that we used were to yield from 0 to 10% drug-loaded gels or the in vitro release studies. The physical state of the drug in these formulations was dissolved up to 4% loading. The 6 - 10% loading of the gel had some drug in suspension form but still used in some of the studies (see **Table 1**) after choosing the 44,000 mol. wt. 50:50 PLGL with the intrinsic viscosity of 0.59 dL/g as the polymer of choice for all our further studies. This was also shown by Dr. Shukla's studies using other drugs such as steroid derivatives used for contraception.

Results of increasing the polymer to plasticizer ratio are shown in **Table 2** to show the best ratio of polymer with a 2% drug loading. These results show that the ratio of 33:67 of polymer to plasticizer yields the best flowable viscous gel with a 2% drug loading. It was therefore decided to use this ratio for all the in vitro release studies.

6. In-vitro release studies:

The results of the in-vitro release studies are described here. **Figure 4** shows the results increasing the drug-loading concentration in the formulation from 0 to 10% carried out in triplicates. **Figure 5** shows the results of varying the polymer:plasticizer ratio on the release of drug from the gel formulations. **Figure 6** shows the amount of plasticizer that is released in these formulations with varying polymer:plasticizer ratios.

Figure 7 shows the results increasing the drug-loading concentration for buprenorphine free base in the formulation containing 33:67 ratio of ATEC:PLGL from 0 to 10% carried out in triplicates as described in previous report. This was carried out using the same system that we had used for buprenorphine hydrochloride to get a direct comparison of release rates (Compare with data in Fig. 4 of Report #1). This shows that the buprenorphine free base is released at a much slower rate than the hydrochloride salt.

This could be explained by the hydrophobicity of the free base which makes it less soluble in aqueous solutions and since it has to partition itself between ATEC and this aqueous solution, it probably gets released a lot slower than the hydrochloride salt. The analysis of the remainder of the gel after 20 days showed that about 90% of the buprenorphine base was still in the gel and that only about 5% had been released during this period.

Figure 8 shows data from studies using buprenorphine hydrochloride at 2% loading and varying the inherent intrinsic viscosity of the polymer, i.e., use the different molecular weight polymer that is available. This was carried out to find a better polymer that would allow the drug to be released faster than the 44,000 mol wt 50:50 PLGL polymer that we had initially chosen for our studies. These studies show that the lower the intrinsic viscosity of the polymer, the greater the amount of drug released. We had decided to use PLGL with the intrinsic viscosity of 0.59 dL/g in our initial studies to get release over longer periods. However, this data shows that the PLGL with the lowest molecular weight, and therefore the lowest intrinsic viscosity, yields gel formulations which allow the buprenorphine hydrochloride to be released much faster than the higher molecular weight polymers.

7. Surface area studies:

Since we know that the surface area of the gel formulation that is exposed to the aqueous medium makes a big difference in the in-vitro studies, we decided that we would modify the special cell to give us a variation of the surface area. We increased the size of the cavity in 2 cells from a diameter of 0.88 cm to 1.25 cm and 1.9 cm leaving the depth of the cavity the same. This gave us surface areas of the gel formulation exposed or in contact with the aqueous medium of 0.66 sq. cm., 1.96 sq. cm. and 2.83 sq. cm respectively. We used these to study the release from buprenorphine hydrochloride and buprenorphine free base drug-loaded gels formulated with the 0.15 dL/g 50:50 PLGL to see what effect the increasing surface area has on the release.

Figure 9 shows the results of increasing the diameter (surface area) of the cell's cavity does lead to increased release of buprenorphine hydrochloride from the gel formulation. These studies were carried out using a 2% drug-loading with polymer intrinsic viscosity of 0.15 dL/g 50:50 PLGL and a 33:67 ratio of polymer:plasticizer and filling the cavities with 240 ul of the gel formulation as before. In the higher diameter cavities, the gel formulation did not fill the cavity to the top. The formulation was not very viscous so immense care had to be taken when filling the bottles with the buffer for the incubation periods.

Figure 10 shows the release of buprenorphine free base as a result of varying the surface area of the gel formulation.

Figure 11 shows the release of Buprenorphine hydrochloride from gel formulations made with PLGL of 0.15dL/g intrinsic viscosity and Triethyl Citrate as the plasticizer with varying surface area of the gel exposed to the buffer. The ratio of the plasticizer:polymer used was 33:67 as this produced more viscous flowable gel than 20:80 ratio which gave very flowable liquid. This ratio was also chosen because all the data from the ATEC studies was done using this ratio and so that the data would have some comparison.

Figure 12 shows data from studies using Triacetin as the plasticizer instead of TEC. Again, we have the similar type of release profile as that obtained from the TEC release study. Also the higher surface area does lead to an increase in release of the drug by a significant amount, about 20% higher.

CONCLUSION & DISCUSSION:

The data generated by these studies have shown that this system consisting of polylactide-co-glycolide (PLGL) polymer, plasticizers such as ATEC, TEC and Triacetin and a solvent can be used to produce injectable buprenorphine hydrochloride and buprenorphine free base. We have also demonstrated from the in-vitro studies that the gels will release the drug into an aqueous medium for a long period of time and so making it possible to use these formulations to design stable biodegradable sustain-release formulations of buprenorphine hydrochloride and free base.

Our results have demonstrated that we can produce injectable gel formulations of buprenorphine that will release the drug for a long period of time, up to 35 - 40 days. However, Capt. Vaughan has pointed out that it may be advantageous to have release of buprenorphine between 48 - 72 hours for the shock trauma patients. We have demonstrated that this system can be optimized to get release of buprenorphine in that time scale.

The system that we have used has a number of variables that can be changed to change the relief profile from an injectable gel. The first and foremost is the polymer itself. There are a number of polymers that have shown to be very effective in yielding control release formulations. We chose PLGL as our consultant who has done a lot of work with this polymer. With the polymer, there are different molecular weights of the polymer which give it a different intrinsic viscosity. We have shown a drastic influence of the release of buprenorphine from a gel formulated with these polymers.

The results here demonstrate that we are getting release profiles for buprenorphine hydrochloride and free base from the gel formulations to be in the shorter time range instead of the 30 - 40 days that we were looking for initially. Using the 0.15 dL/g 50:50 PLGL (average molecular weight 11,400) has provided gel formulations which allow the drug to be released much faster. Buprenorphine free base does not get released as well as the hydrochloride salt and that could be due to its hydrophobic nature.

The system also utilizes a plasticizer and we have studied three of a number that are available. Again, the choice of using these plasticizers were based on their solubility in water and the solubility of the drug in these plasticizers. The ones we used, namely, ATEC, TEC and Triacetin have shown that there is a significant amount difference between these plasticizers.

Initial studies we conducted were based on using ATEC as the solvent and this yielded gels that had a release profile that was not acceptable, i.e., 35 - 40 days. In the meantime, we had contacted Morflex Inc. who manufactures FDA approved plasticizers and requested them to suggest other plasticizers than ATEC which have a higher aqueous solubility than ATEC which we have used in our studies. They suggested some other plasticizers which we have investigated, namely, Triethyl Citrate and Triacetin which

have worked well. We have also considered that other plasticizers or even mixing two of these would yield the right release profile of the drug.

The results here demonstrate that we are getting release profiles for buprenorphine hydrochloride within 24 - 144 hours with about 30% residual drug still in the gel by using TEC and /or Triacetin as our plasticizer instead of the ATEC that we initially used.

We have also demonstrated that the ratio of the polymer:plasticizer plays a major role in the release of the drug from these formulations. The higher the plasticizer the faster the drug is released in the initial phase as it probably co-elutes with the plasticizer. In the later stages where the drug is primarily entrapped in the polymer without any plasticizer, the release becomes much slower. This is then dependent on the rate of the breakdown of the polymer and not diffusion of the drug with the plasticizer. **Figure 13** shows some of these possible mechanisms.

Using polymer:plasticizer ratio of 20:80 instead of 33:67 that we have used with the 0.15dL/g polymer. This combination made a very flowable liquid and we have to find a better way of studying the release from these "gels" which we will discuss with both Dr. Shukla and Capt. Vaughan.

We have also demonstrated that using a lower polymer:plasticizer ratio also leads to faster release of buprenorphine hydrochloride (Fig. 5). Therefore, it was decided to test drug release from gels formulated with 50:50 PLGL of intrinsic viscosity of 0.15 dL/g and polymer:plasticizer ratio of 20/80 instead of 33/66. There was a small problem with this in that the formulation was a flowable liquid and not a viscous gel. This presented a few difficulties in using this formulation in our in-vitro release gels as the cells we have designed are better with gels than flowable liquids. For this reason, our studies with the polymer of 0.15 dL/g intrinsic viscosity, we still used the 33/66 ratio of the polymer:plasticizer. This gave a viscous liquid which we could handle better.

Capt. Vaughan has also been helpful in suggesting various other ways to study release from less viscous or the "very flowable" gels. However, Dr. Shukla has not felt comfortable with the method used by Atrix of dropping the liquid/gel directly into the release buffer as this method does not allow the ability to control the surface area of the gel exposed to the release buffer. Also the gel could be disturbed very easily when changing the buffer.

The other suggestion that Capt. Vaughan had and that we have also thought about was using dialysis bags. However, having a dialysis bag also introduces another variable that may retard the free flow of the drug. The other problem with this is that the gel hardens as the plasticizer is removed and this clogs the pores in the dialysis tubing. This is also the reason that we have not used dialysis tubing over our cell to prevent the gel from flowing out.

The data also has shown with all three different plasticizers that an increase in the exposed surface area of the gel to the release buffer does lead to faster and greater release of the drug. This should mean that in-vivo release rates should be greater than in-vitro since both the surface area of the exposed gel will be bigger and the PLGL will also be broken down in the body. The breakdown of the PLGL will lead to release of the drug from the residual gel as well as in the initial phase where the drug is released with the plasticizer leaching out from the gel.

These studies show that increasing the surface area does help in allowing the drug to be released faster (fig.9 - 12). Buprenorphine free base still is released at a slower rate than the hydrochloride salt even in the 0.15 dL/g 50:50 PLGL. The increased release rate for the buprenorphine hydrochloride with the increased surface area still is not enough to release the drug in 3 - 4 days.

The release of buprenorphine hydrochloride from these gels is faster in the initial phase but then does slow after about 36 hours. This may be explained by the initial release from the gel due to release of the drug that is dissolved in the TEC with the TEC partitioning out into the buffer. The drug that does not get released with this initial rapid rate then gets entrapped in the polymer and will be released at a much slower rate. The release profile seems almost biphasic.

The DSC results of the DSC studies were included as this instrument was now available in Dr. Shukla's lab and it was some extra data that we wanted to include for our characterization of our gels. This may not have any relevance or significance at room temperatures where our studies take place but it does give some reasonable way of analyzing what is happening to these gels and may provide valuable data for the characteristic of these gels.

We also decided to concentrate on just using buprenorphine hydrochloride for later studies with the different plasticizers as we had more experience with it and that the buprenorphine free base is not available commercially. We should be able to do some work with the free base in Phase II after getting more information about blood levels for both the hydrochloride salt and the free base. Furthermore, in-vitro studies as carried out are very dependent upon the surface area of the exposed gel and with our cells, this area is fairly small. We also know that the polymer PLGL breaks down in the body within 30 - 90 days depending on its intrinsic viscosity. The lower the intrinsic viscosity, the faster it breaks down. However, our in-vitro studies cannot mimic these conditions and so our in-vitro release rates would be slower than the in-vivo release rates. We can choose our formulation parameters with these in-vitro tests to optimize our release rates with this in mind.

We still intend to carry out some preliminary in-vivo experiments with one of the gel formulations that we have tested to show how the in-vivo release rates compare with the in-vitro results. We feel that the extra data, especially from the in-vivo studies will help us to optimize this system not only for Buprenorphine HCl but also other drug molecules.

Figure 1. Special teflon cell for in-vitro drug release studies
 Cavity dimensions are 0.88 cm diam, 0.4 cm deep
 and holds 240 mg of gel formulaion.

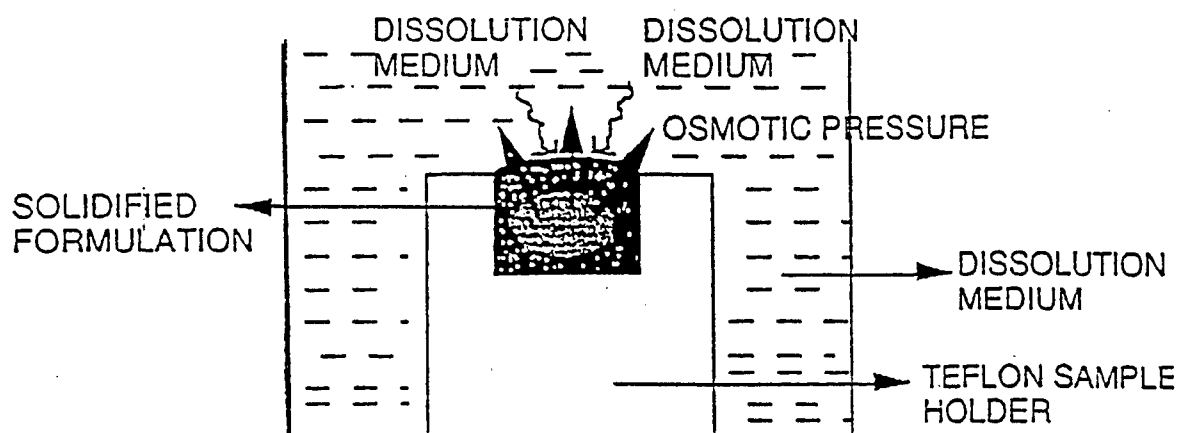
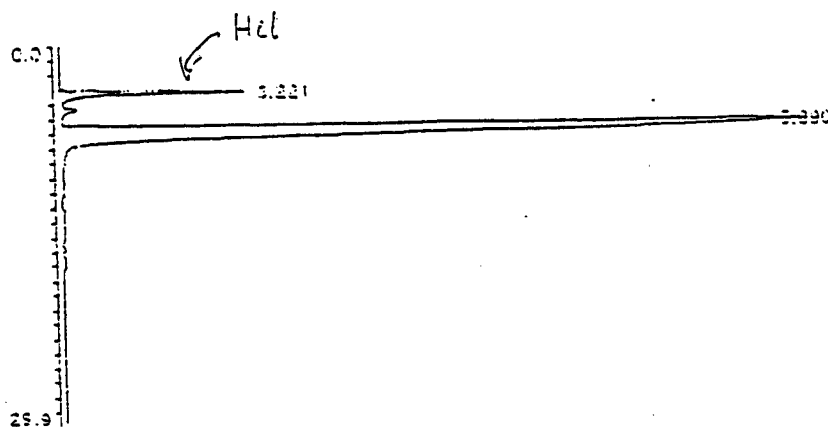


Figure 2. HPLC chromatogram of Buprenorphine hydrochloride.

Sample: Product: B-117/WACH-
 Mobile Phase: 50% KH₂PO₄ (0.05M)/CH₃CN/HCl
 Flow Rate: 0.8 ml/min, Conc.: 0.4 mg/ml in m.p.
 Column: Bondclone C18
 Detector: LDC/280 nm

Inject Vol: 20
 Sampling Int: 0.1 Seconds

Chromatogram:



Analysis: Channel 2

Peak No.	Time	Type	Height(μV)	Area(μV-sec)	Area%
1	3.221	N	40805	524176	8.169
2	29.900	N	151097	5391909	81.833
Total Area:				6416085	100.002

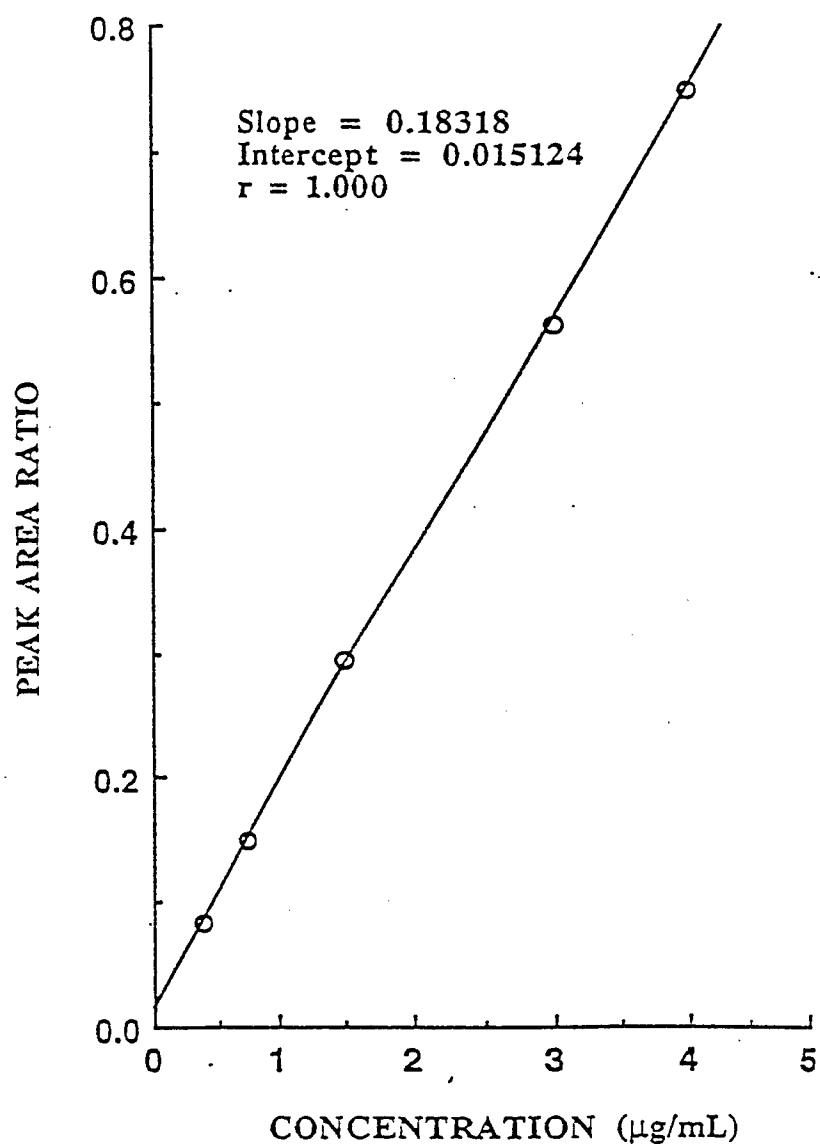


Figure 3. A typical HPLC standard curve for the assay of buprenorphine hydrochloride samples.

Table 1. Physical state of formulations containing varying drug loadings

Drug Loading (w/w)	Physical State of the Formulation*	Physical State of Drug in the Formulation*
1 %	Viscous liquid	Dissolved
2 %	Viscous liquid	Dissolved
4 %	Viscous liquid	Suspended
6 %	Viscous liquid	Suspended
8 %	Viscous liquid	Suspended

* 33% of 50/50 polylactide-co-glycolide (IV = 0.59 dL/g) and 67% NMP

Table 2. Physical state of formulations containing varying polymer:plasticizer ratios

Polymer:plasticizer ratio	Physical State of the Formulation	Physical State of Drug in the Formulation
20 : 80	Very flowable liquid	Dissolved
40 : 60	Viscous liquid	Dissolved initially; however precipitated partially after 48 hrs
50 : 50	Flowable gel	Suspended
60 : 40	Flowable gel	Suspended
80 : 20	Thick paste	Suspended

* 50/50 Polylactide-co-glycolide (IV=0.59 dL/g)
Drug loading = 2% w/w

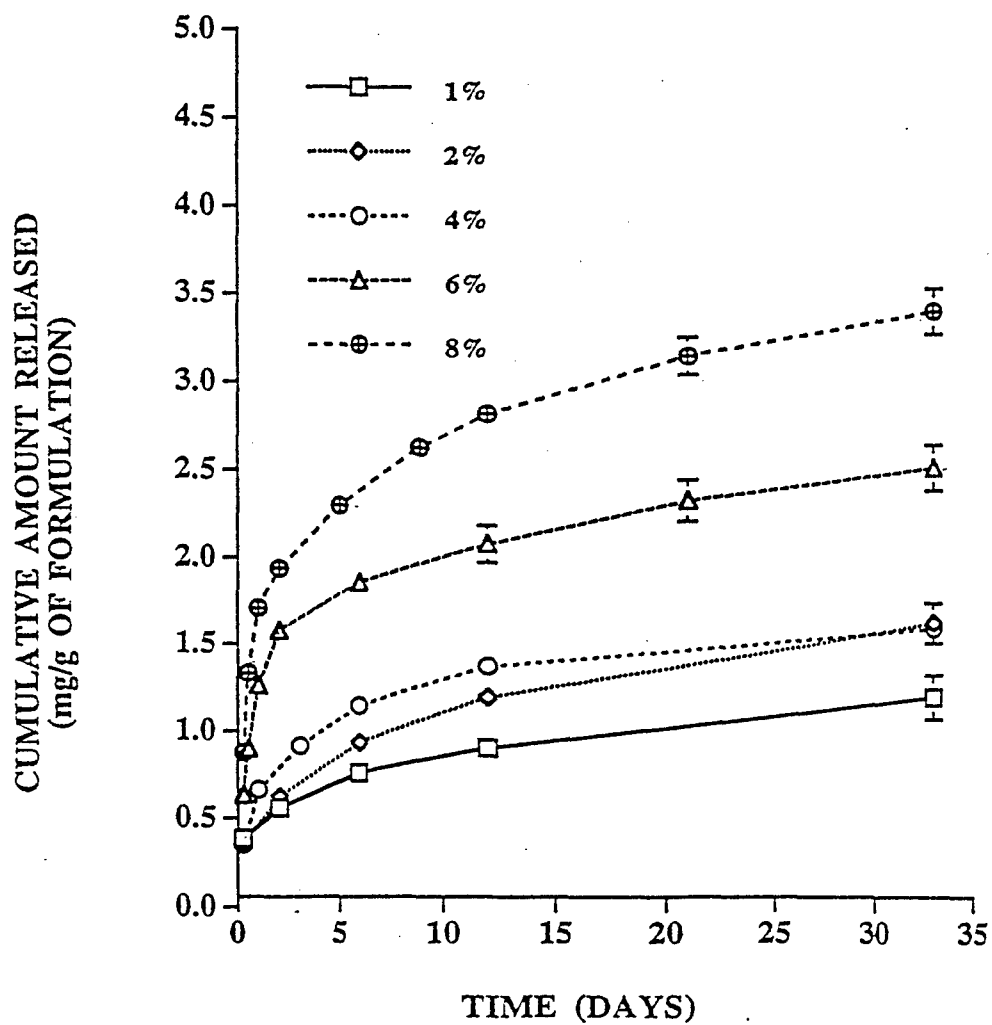


Figure 4. Effects varying drug loading on cumulative amount of buprenorphine released. Polymer - 50/50 PLGL mol. wt. 44,000 (IV = 0.59):Plasticizer - ATEC of 33:67.

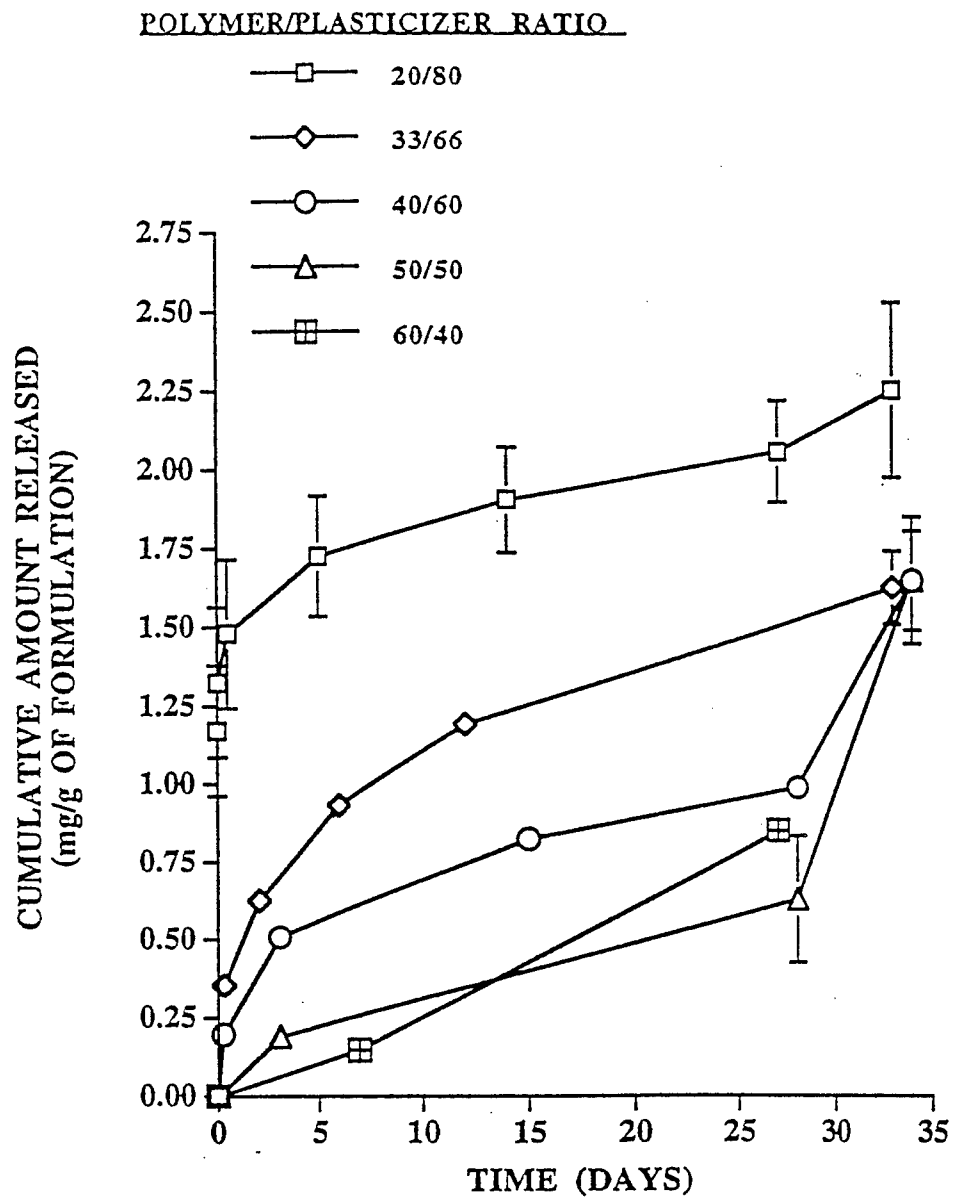


Figure 5. Effect of varying polymer:plasticizer ratios on cumulative amount of drug released. Polymer - 50/50 PLGL (IV = 0.59)
Plasticizer - ATEC, drug-loading - 2%

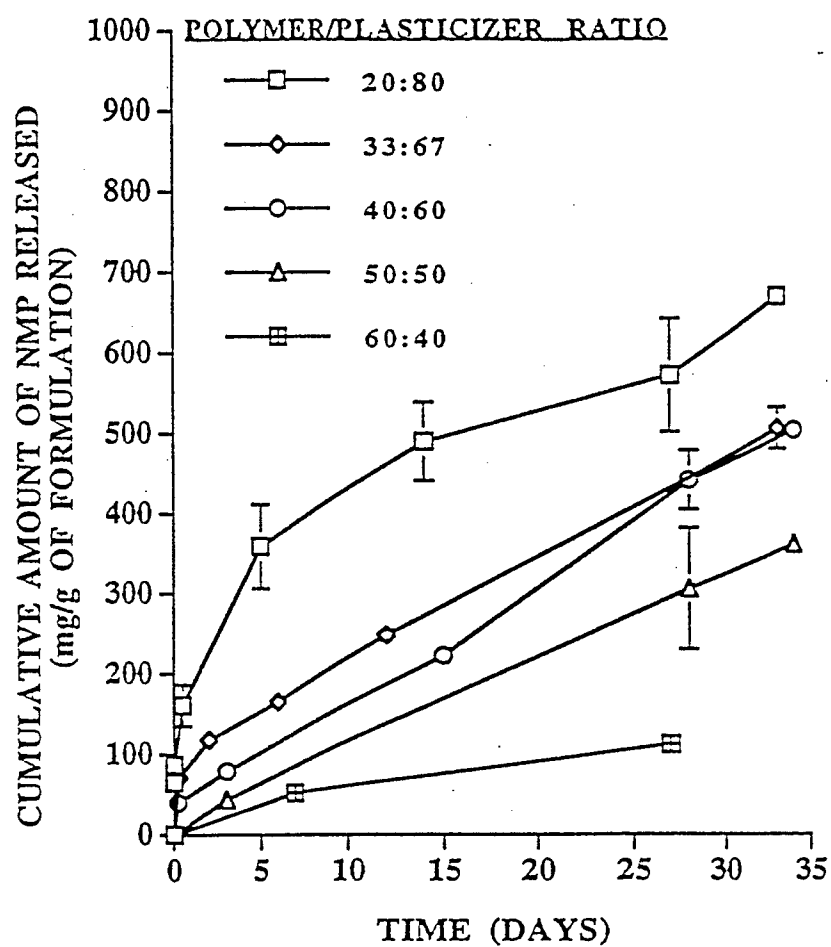


Figure 6: Effect of varying polymer:plasticizer ratios on cumulative amount of plasticizer released. Polymer - 50/50 PLGL (IV = 0.59)
Plasticizer - ATEC, drug-loading - 2%

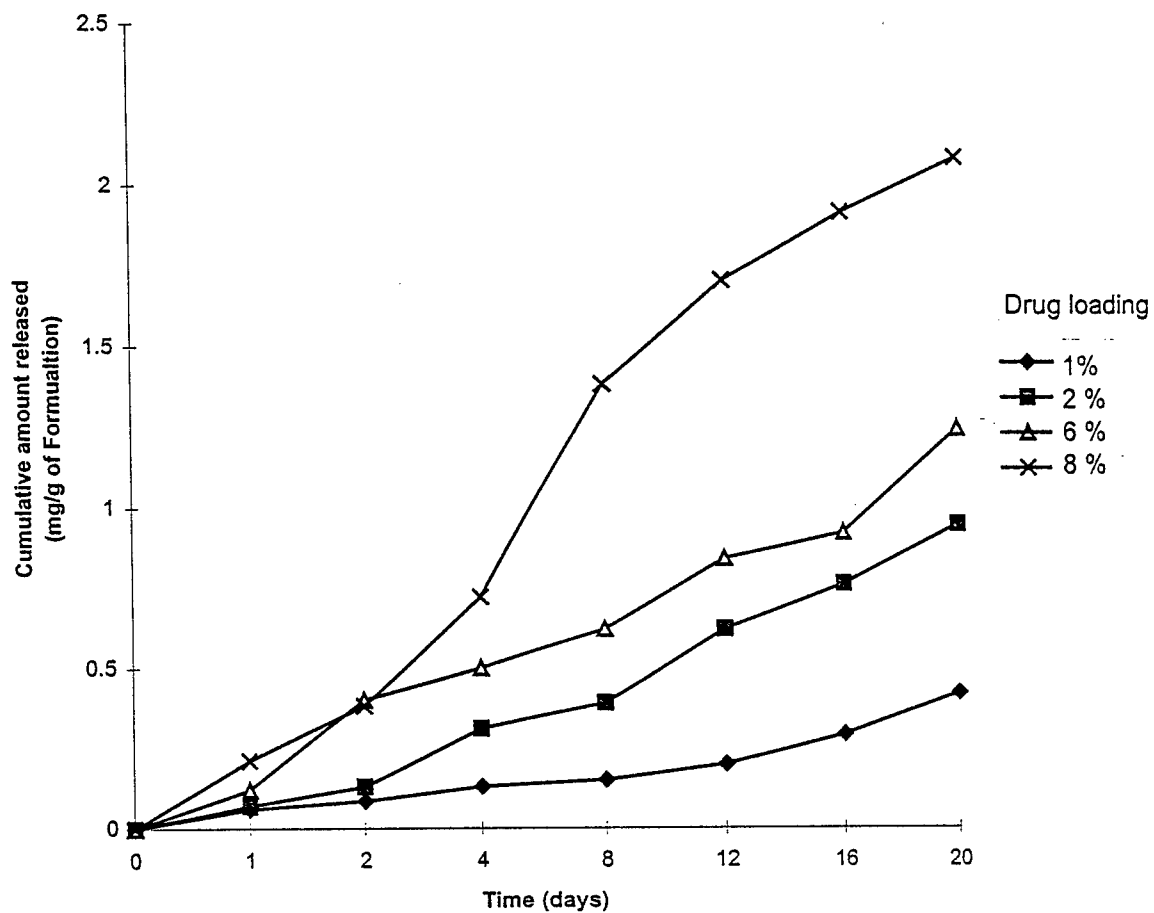


Figure 7. Effects varying drug loading on cumulative amount of buprenorphine free base released. Polymer - 50/50 PLGL mol. wt. 44,000 (IV = 0.59);Plasticizer - ATEC of 33:67.

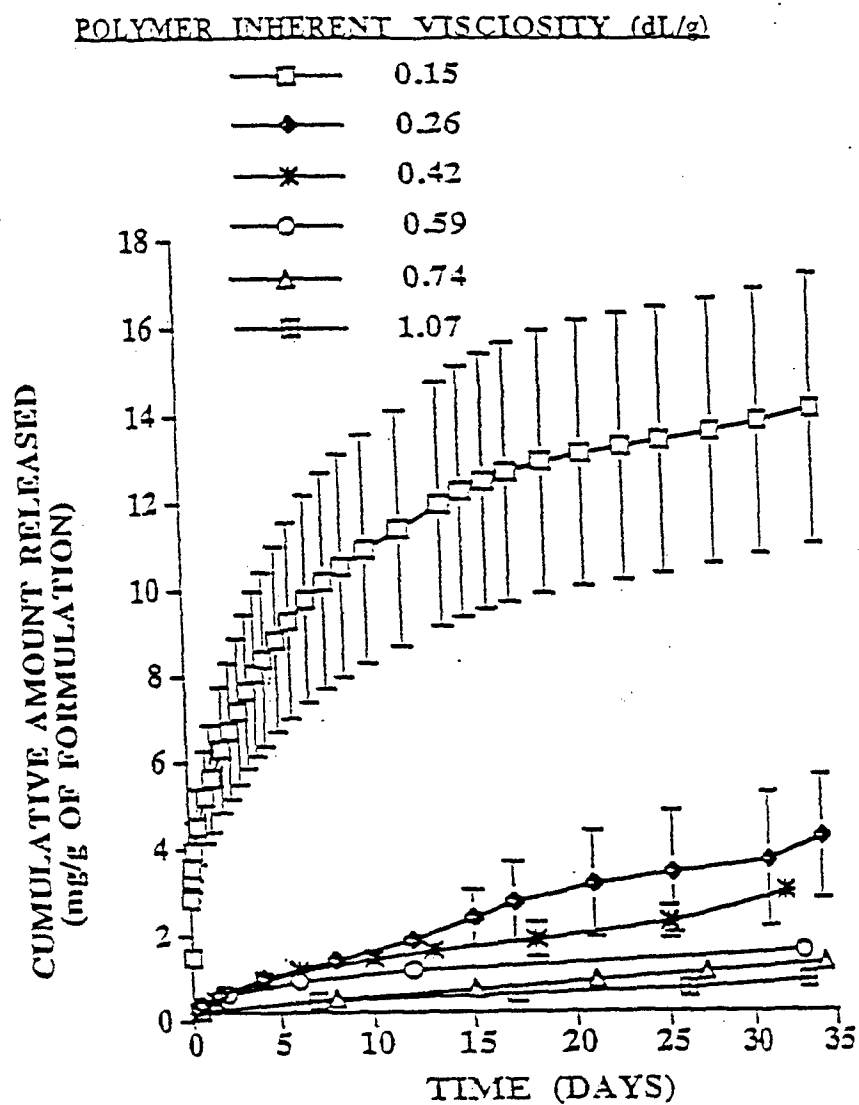


Figure 8. Effects varying inherent viscosities on cumulative amount of buprenorphine HCl released. Polymer - 50/50 PLGL mol. wt. 44,000 (IV = 0.59):Plasticizer - ATEC of 33:67. Drug loading 2%

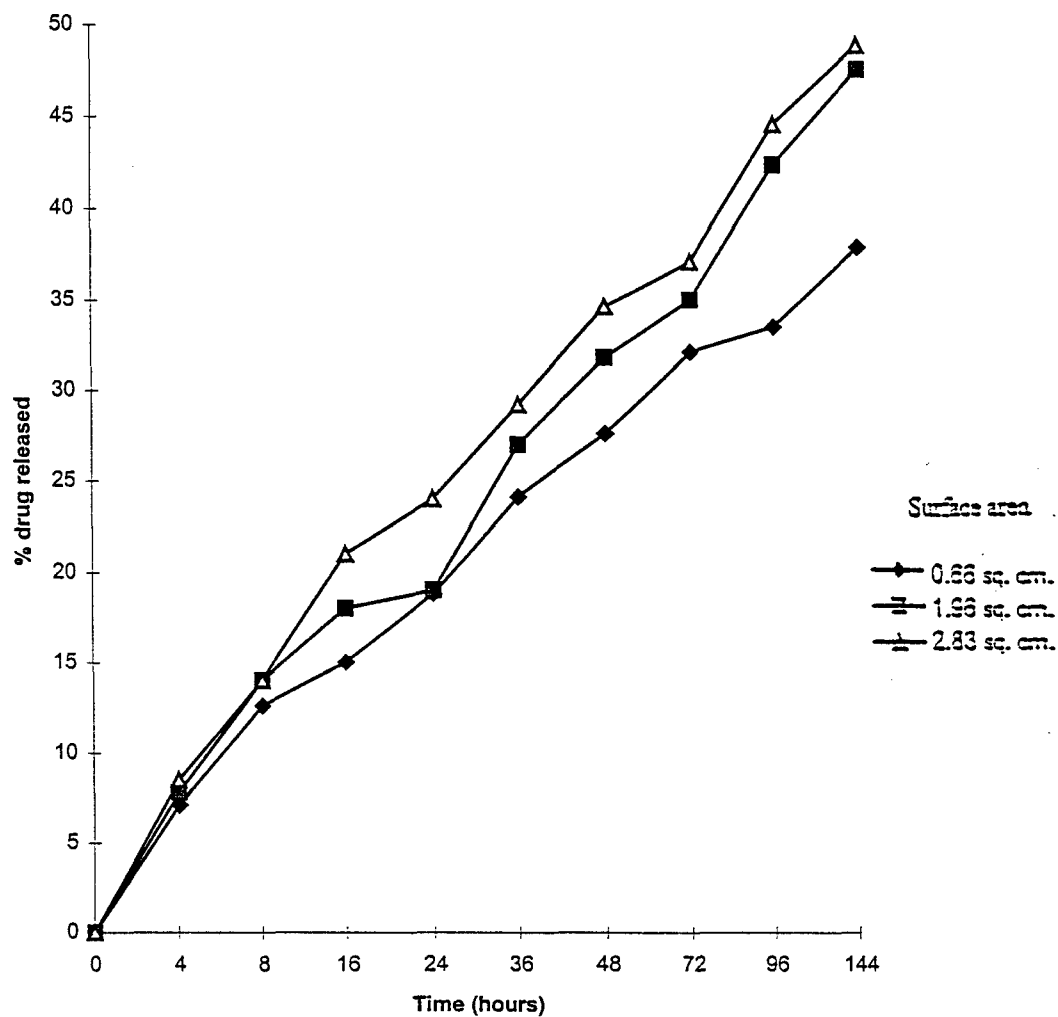


Figure 9. Effects varying surface area on cumulative amount of buprenorphine hydrochloride released. Polymer - 50/50 PLGL mol. wt. 44,000 (IV = 0.59):Plasticizer - ATEC of 33:67. Drug loading 2%

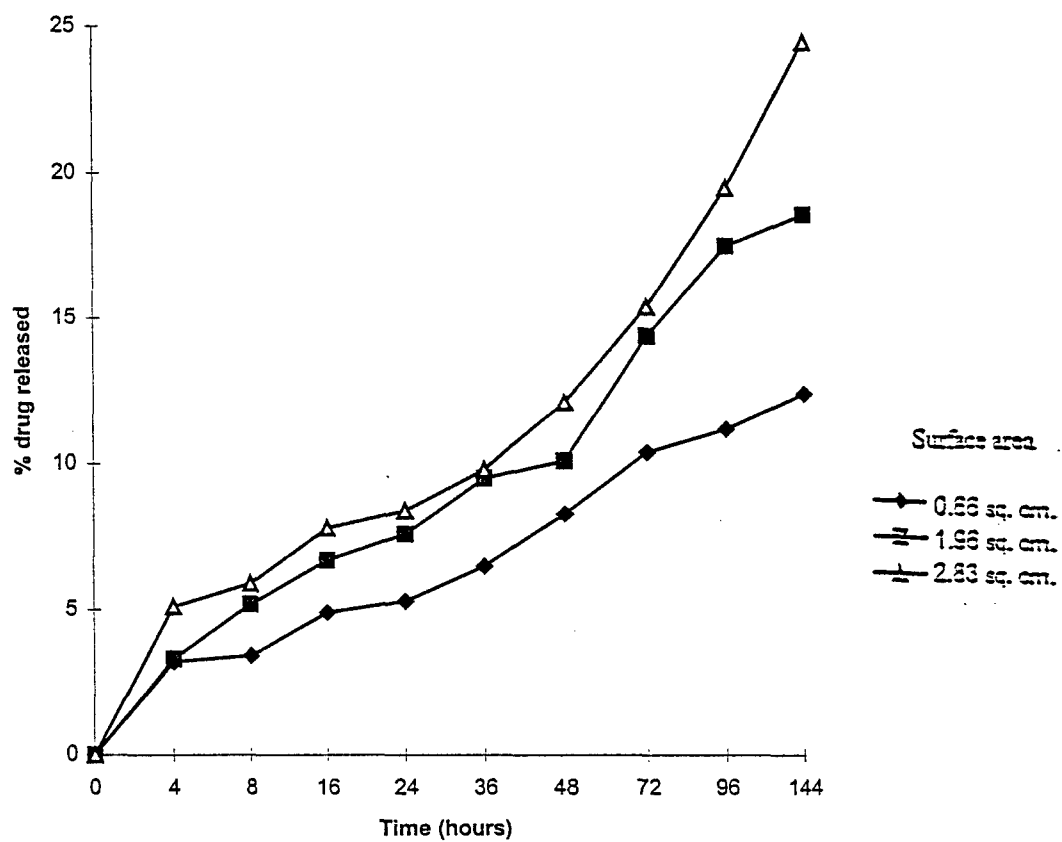


Figure 10. Effects varying surface area on cumulative amount of buprenorphine free base released. Polymer - 50/50 PLGL mol. wt. 44,000 (IV = 0.59):Plasticizer - ATEC of 33:67. Drug loading 2%

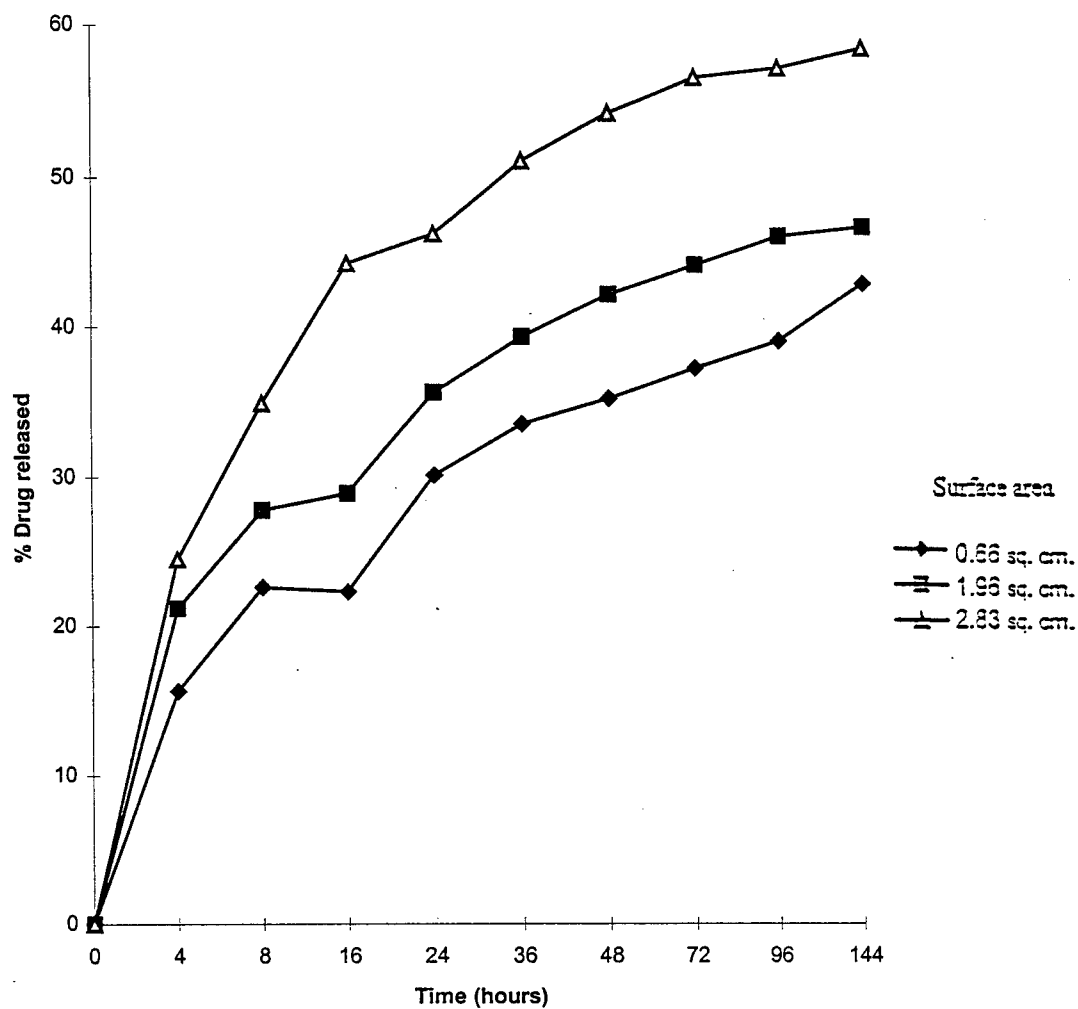


Figure 11. Effects varying surface area on cumulative amount of buprenorphine hydrochloride released from TEC gel. Polymer - 50/50 PLGL mol. wt. 11,400 (IV = 0.15):Plasticizer - TEC of 33:67. Drug loading 2%

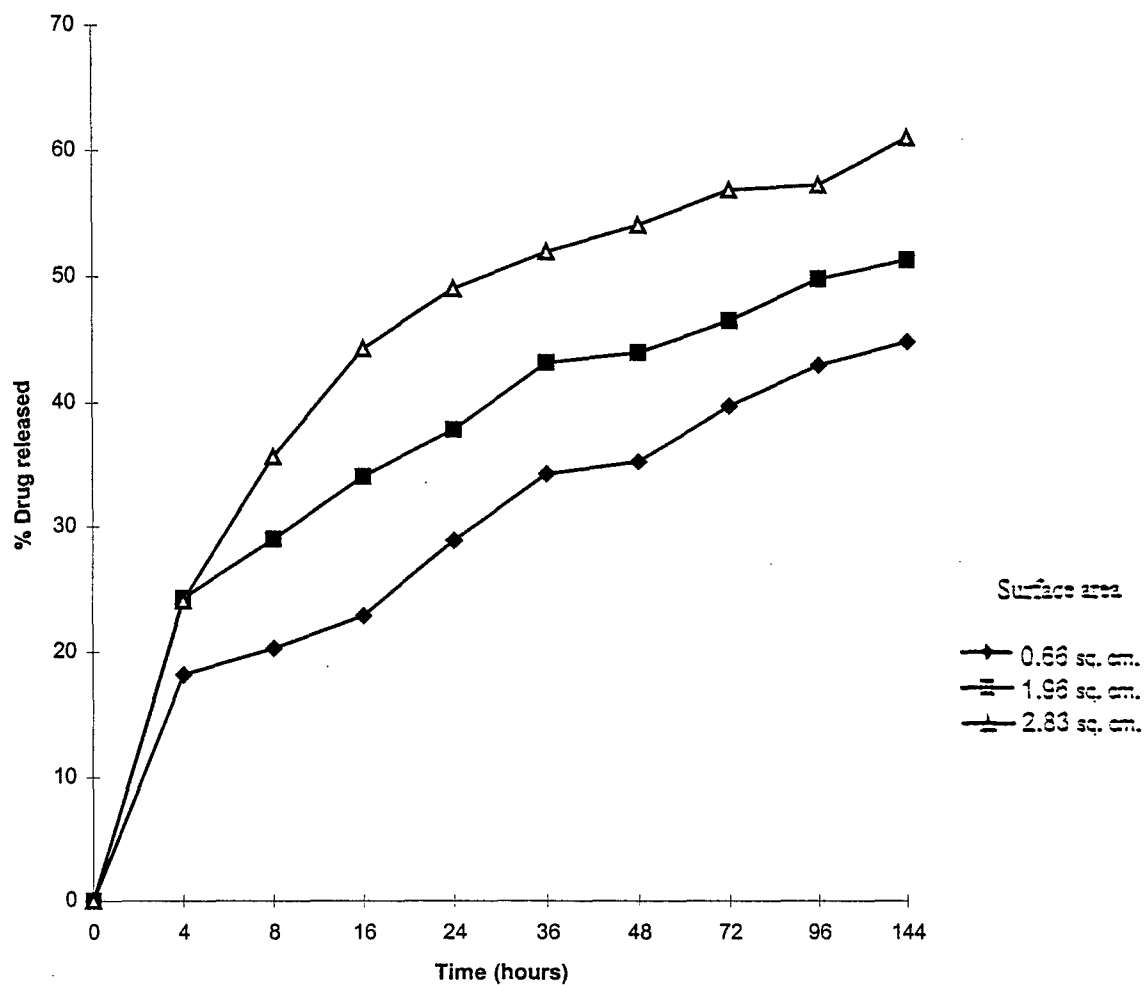
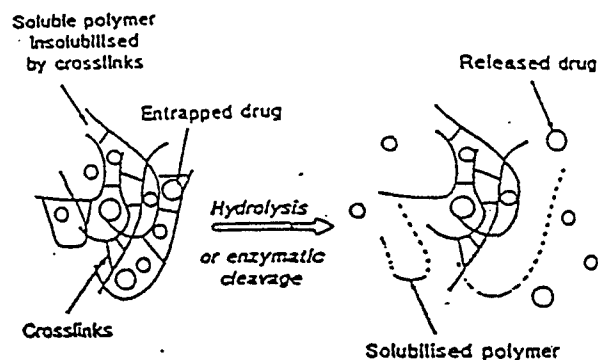
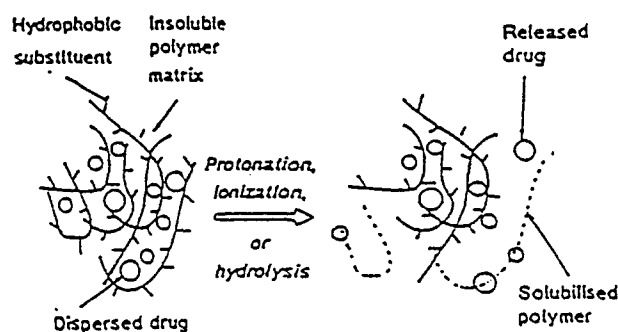


Figure 12. Effects varying surface area on cumulative amount of buprenorphine hydrochloride released from TRIACETIN gel. Polymer - 50/50 PLGL mol. wt. 11,400 (IV = 0.15):Plasticizer - TEC of 33:67. Drug loading 2%

Mechanism I



Mechanism II



Mechanism III

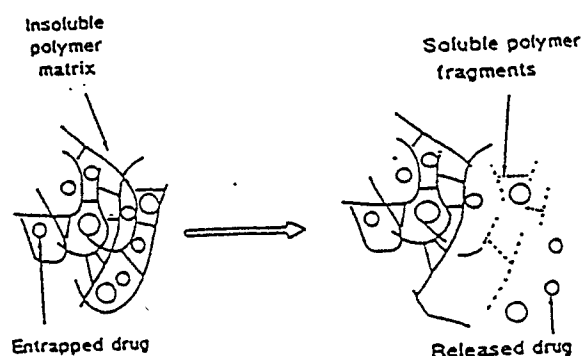


Figure 13. Mechanisms of degradation of biodegradable polymers.

Mechanism I - a biodegradable polymeric matrix insolubilised by degradable polymer crosslinks; Mechanism II - a bioerodible polymeric matrix solubilised by protonation, ionization or hydrolysis; Mechanism III - a bioerodible polymeric matrix solubilised by backbone cleavage

Source: Danckwerts M. and Fassihi A. Implantable controlled release drug delivery systems: a review. *Drug Development and Industrial Pharmacy*, 17(11): 1465-1502 (1991) (by permission).

Personnel involved in this project:

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- 2. Atul Shukla, PhD - Consultant**
- 3. Smuti Patel - Technician**
- 4. Mary Daher - Secretary**



DEPARTMENT OF THE ARMY
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REPLY TO
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4 Dec 02

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Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir,
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